## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study |
| **AUTHORS** | Wang, Mei; Paterson, Michael; Thabane, Lehana; Siegal, Deborah; Mbuagbaw, Lawrence; Targownik, Laura; Holbrook, Anne |

## VERSION 1 – REVIEW

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| **REVIEWER** | Eue-Keun Choi<br>Seoul National University College of Medicine |
| **REVIEW RETURNED** | 04-Nov-2021 |

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| **GENERAL COMMENTS** | This article is a study protocol for the association of DOAC-PPI co-therapy with adverse outcomes using a population-based cohort database. The study will use claims database and other multiple healthcare data in Ontario, Canada's most populous province. The protocol is well-written and provides sufficient details to define and conduct the actual study. Descriptions of data sources, data analysis, sample size calculation, and definitions of concepts or covariates are well written. However, there exist a few issues that need to be clarified for this study.<br><br>1. The study design is to compare the effectiveness and safety between a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). The main effect of PPI co-therapy would be reducing the risk of upper GI bleeding. However, the primary outcome of this study is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. It would be better to define the primary outcome as GI related events, and the composite of clinically relevant bleeding, thrombotic events, or all-cause death would be the secondary outcome. Please consider the study design as the COGENT trial (PMID: 20925534).<br>2. It is unclear how to perform the analysis if there exist different values of the same covariates across various database if the authors decided to use multiple database for the study.<br>3. Please describe how to handle the concomitant drugs which have similar GI protective effect.<br>4. Operational definitions of covariates need more details. For example, would the authors define a patient have atrial fibrillation if he/she had a "single" disease code in medical history? Would the disease code occur during outpatient and inpatient clinics treated identically?<br>5. The flowchart of the study population may help readers understand the protocol precisely.<br>6. The review recommends the authors should include pre-specified subgroup analyses such as subgroups by doses/categories of DOAC and those with low vs. high risk of bleeding. |

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| **REVIEWER** | Stefano Skurzak<br>Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici |
| **REVIEW RETURNED** | 11-Nov-2021 |

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| **GENERAL COMMENTS** | Dear Authors,<br><br>The study protocol proposed by Dr. Wang Mei is a well described plan for large population based cohort study on the effects of direct oral anticoagulant (DOACs) and proton pump inhibitors (PPIs) co-prescription.<br><br>I have got some major observations to the study:<br><br>The choice of a composite outcome that includes opposite complications (bleeding and thrombosis) and death should be better explained in terms of rationale and analysis.<br><br>The co-therapy cohort (DOACs+PPIs) is presumed to be at higher risk for (gastrointestinal GI) bleeding with respect to the control cohort (DOACs alone). This would drive the results to an increased risk for co-prescription vs single DOACs prescription and this would hardly be balanced by weighting the sparse covariates assessing the risk for bleeding (history of bleeding in HASB_ED score and hepatic disease in comorbidities). When a doctor prescribes PPIs, He bears in mind the possibility of bleeding as a consequence of gastric ulcers (at least in part of the patients) even if there is a common belief that PPI are generally over prescribed also in low risk patients. Why a control cohort of only PPI patients is not included in the study? Indeed, while the complication “thrombotic events” is adequately covered by a pure DOACs cohort, a “at risk of (GI) bleeding” cohort is not lacking.<br><br>There will be a number of patients that discontinues PPIs while maintaining DOACs in real life situations. Can these patients be used as (crossover) controls for the outcome of interest? Obviously the numbers will be more limited.<br><br>Data on single physician’s attitude toward co-prescription are not included. I think that They could be useful in understanding the effects of combining PPIs with DOACs on outcomes (eg. Physician one nearly always co-prescribe PPIs and DOACs and we can argue that a potential for over-prescription induces different outcomes versus under-prescription) and interesting insights on co-prescription psychology.<br><br>Data about the occurrence of sequential outcomes (eg. first bleeding then thrombosis due to reduction of anticoagulation and finally the eventual death of the patient) should be ideally reported notwithstanding the approach of “whichever occurs first” adopted for the analysis of data (Page 5 lines 50-52). |

**VERSION 1 – AUTHOR RESPONSE**

| **Reviewer 1: Dr. Eue-Keun Choi, Seoul National University College of Medicine** | |
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| 1. The study design is to compare the effectiveness and safety between a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). The main effect of PPI co-therapy would be reducing the risk of upper GI bleeding. However, the primary outcome of this study is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. It would be better to define the primary outcome as GI related events, and the composite of clinically relevant bleeding, thrombotic events, or all-cause death would be the secondary outcome. Please consider the study design as the COGENT trial (PMID: 20925534). | As we outline in the introduction section, the indirect evidence for PPIs for treating gastroesophageal reflux disease and GI bleeding has been used to support its concomitant use with DOACs. There is no randomized trial evidence supporting or refuting the use of PPIs with full dose DOACs. The objective of the present study is to examine the effects of concomitant PPIs on a number of key risks and benefits in DOAC-treated patients. Therefore, we decided to use a composite endpoint (clinically relevant bleeding, thromboembolic events, and death) as our primary outcome for two main reasons: 1) each of the outcomes is of major importance to both clinicians and patients and 2) it provides a summary estimate with greater precision, of overall harm versus benefit to the patient. |
| 2. It is unclear how to perform the analysis if there exist different values of the same covariates across various database if the authors decided to use multiple databases for the study. | The ICES Data Repository consists of record-level, coded, and linkable databases. A single, study-specific dataset will be constructed that combines the source administrative databases with investigator-defined patient characteristics, drug exposures and outcome measures. While alternate definitions are possible for some characteristics, we have selected what we believe are the optimal definitions for the setting given the data that are available to us. The details of our approach are found in Table 2. |
| 3. Please describe how to handle the concomitant drugs which have similar GI protective effect. | Thank you for pointing this out. Histamine H2 receptor antagonists, including cimetidine, famotidine, nizatidine sucralfate, and ranitidine, will be identified and treated as a separate covariate (page 7, lines 199-200). |
| 4. Operational definitions of covariates need more details. For example, would the authors define a patient have atrial fibrillation if he/she had a “single” disease code in medical history? Would the disease code occur during outpatient and inpatient clinics treated identically? | As noted in our response to Question 2, the operational definitions for covariates are provided in Table 2 |
| 5. The flowchart of the study population may help readers understand the protocol precisely. | We agree and have supplied a flowchart (Figure 1). |
| 6. The review recommends the authors should include pre-specified subgroup analyses such as subgroups by doses/categories of DOAC and those with low vs. high risk of bleeding. | We agree with this suggestion. Subgroup analyses will be undertaken by DOAC (see page 8, lines 236-237). The HAS-B_ED Score will be used to adjust for bleeding risk in our analyses. |
| **Reviewer 2: Dr. Stefano Skurzak, Ospedale San Giovanni Battista** | |
| 1. The choice of a composite outcome that includes opposite complications (bleeding and thrombosis) and death should be better explained in terms of rationale and analysis. | Please refer to our response to Question one from Reviewer 1. |
| 2. The co-therapy cohort (DOACs + PPIs) is presumed to be at higher risk for (gastrointestinal GI) bleeding with respect to the control cohort (DOACs alone). This | We agree that patients prescribed PPIs in this cohort are likely to be at increased risk of GI bleeding events. One of the key limitations of any observational study is the risk of residual confounding, even after all potential |

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| would drive the results to an increased risk for co-prescription vs single DOACs prescription and this would hardly be balanced by weighting the sparse covariates assessing the risk for bleeding (history of bleeding in HASB_ED score and hepatic disease in comorbidities). When a doctor prescribes PPIs, He bears in mind the possibility of bleeding as a consequence of gastric ulcers (at least in part of the patients) even if there is a common belief that PPI are generally over prescribed also in low-risk patients. Why is a control cohort of only PPI patients not included in the study? Indeed, while the complication "thrombotic events" is adequately covered by a pure DOACs cohort, a "at risk of (GI) bleeding" cohort is not lacking. | adjustments are made. This will be listed as a limitation in the results papers. One of the positive features of our design is the time-varying analysis, where periods on versus off PPI therapy will be precisely identified. This will reduce bias. We note that the reviewer refers to an example doctor as 'he' but we are unaware of any sex-specific prescribing data that we need to incorporate.<br><br>Since our study population is patients taking DOACs and their risk of important adverse events while taking PPIs versus not, there is no role for any PPI-only group. In other words, this is a drug interaction study. |
| 3. There will be a number of patients that discontinues PPIs while maintaining DOACs in real life situations. Can these patients be used as (crossover) controls for the outcome of interest? Obviously, the numbers will be more limited. | Yes, because the study drug exposures are time-varying, both exposed and unexposed person-time will be accounted for. |
| 4. Data on single physician's attitude toward co-prescription are not included. I think that They could be useful in understanding the effects of combining PPIs with DOACs on outcomes (e.g., Physician one nearly always co-prescribe PPIs and DOACs and we can argue that a potential for over-prescription induces different outcomes versus under-prescription) and interesting insights on co-prescription psychology. | While we agree that physicians' attitudes toward the co-prescription of DOAC and PPI is worthy of study, this is well beyond the scope of our health database study. |
| 5. Data about the occurrence of sequential outcomes (e.g., first bleeding then thrombosis due to reduction of anticoagulation and finally the eventual death of the patient) should be ideally reported notwithstanding the approach of "whichever occurs first" adopted for the analysis of data (Page 5 lines 50-52). | We agree entirely with the reviewer about the clinical occurrence of adverse event cascades in some patients, just as is described. We understand that leading observational research methodologists continue to work on analytic methods to be able to accomplish the high degree of complexity. However, validated methods are not yet available, and the universally accepted approach currently is to count the first outcome that occurs. In this study, endpoint-specific analyses will be undertaken with censorship on death, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance, or the end of the study period (31 March 2020), whichever occurs first. We hope that the sequential analysis suggested, is possible to perform in the future. |

**VERSION 2 – REVIEW**

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| **REVIEWER** | Stefano Skurzak<br>Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici |
| **REVIEW RETURNED** | 24-Jan-2022 |

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| **GENERAL COMMENTS** | Dear Editor and authors, |

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| | the authors discuss some of the suggestions raised in the first round of review but kept their positions. In particular two points remain controversial in my opinion:<br><br>“This is an interaction study”<br><br>Conceptually while studying the effect of co-prescription of a drug A and drug B it would be interesting to know the prevalence of adverse events/outcomes with drug A and drug B alone in the same population at the same time. Relying only on literature data on the effects of PPI alone on hemorrhagic complications introduces a less straightforward interpretation of main results. The framework of the proposed analysis contains already all the structure to obtain such data. Anyway these data are not strictly necessary and the time-varying analysis provide some more insight in the main analysis.<br><br>Physiscian’s attitude toward co-prescription<br><br>Simple raw data about the attitude of physicians toward co-prescription could be eventually obtained from the ratio between number of patients with a DOAC prescription and the number of patients with a DOAC-PPI co-prescription. This is a very rudimental approach but I think potentially informative on the effect of co-prescription on main outcomes. The authors mentioned the ICES Physician Database (IPDB) but it is not clear what kind of information They will extract from this database.<br><br>The study proposal is acceptable and I understand well the difficulties of conducting such large population based studies. However I still feel that unmeasured variables will drive the results of the study towards an increased (biased) risk of unwanted (composite) outcomes in the co-prescription group.<br><br>Kind regards |

**VERSION 2 – AUTHOR RESPONSE**

| **Reviewer 2: Dr. Stefano Skurzak, Ospedale San Giovanni Battista** | |
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| the authors discuss some of the suggestions raised in the first round of review but kept their positions. In particular two points remain controversial in my opinion:<br><br>"This is an interaction study"<br><br>Conceptually while studying the effect of co-prescription of a drug A and drug B it would be interesting to know the prevalence of adverse events/outcomes with drug A and drug B alone in the same population at the same time. Relying only on literature data on the effects of PPI alone on hemorrhagic complications introduces a less straightforward interpretation of main results. The framework of the proposed analysis contains already all the structure to obtain | We appreciate the reviewer's understanding of our research scope and question. While we agree that it might be interesting to study a 'PPI-only' arm, the time-varying analysis is already very complex, and our research question is straightforward that we are interested in the difference in important outcomes between patients on DOACs alone versus DOACs plus PPI. |

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| such data. Anyway, these data are not strictly necessary, and the time-varying analysis provide some more insight in the main analysis. | |
| Physician's attitude toward co-prescription<br><br>Simple raw data about the attitude of physicians toward co-prescription could be eventually obtained from the ratio between number of patients with a DOAC prescription and the number of patients with a DOAC-PPI co-prescription. This is a very rudimental approach, but I think potentially informative on the effect of co-prescription on main outcomes. The authors mentioned the ICES Physician Database (IPDB), but it is not clear what kind of information They will extract from this database. | This is an interesting suggestion, but the ratio of patients in a physician practice in Canada tells us much more about the risk category of the patient than it does about physician attitudes towards prescribing. For example, Internal Medicine and Gastroenterology will see patients at much higher risk of bleeding events.<br><br>Unfortunately, the IPDB contains rudimentary information about physicians practicing, including demographic information about each physician (i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained, and graduation year. Therefore, we only use this database to identify patients likely to have received cancer-related radiation by using billing data of Radiation Oncologists. |
| The study proposal is acceptable, and I understand well the difficulties of conducting such large population-based studies. However, I still feel that unmeasured variables will drive the results of the study towards an increased (biased) risk of unwanted (composite) outcomes in the co-prescription group. | We agree that one of the key limitations of any observational study is the risk of residual confounding, even after all potential adjustments are made. We hope to decrease this by our use of time-varying analysis but agree that it may be a problem. Therefore, we added this as a limitation in the current manuscript (page 7, lines 209-210). |